

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. (Currently Amended) An isolated anti-angiogenic polypeptide or peptide selected from the group consisting of:

- (a) a conservative amino acid substitution variant of SEQ ID NO:5 or SEQ ID NO:6 having substantially the same transition metal ion- or plasminogen- binding activity or substantially the same biologic activity as a polypeptide of the sequence SEQ ID NO:5 or SEQ ID NO:6; and
- (b) a pentapeptide consensus subsequence from SEQ ID NO:5 or 6 consisting of
 - (i) the sequence (His,Pro)-(His,Pro)-Pro-His-Gly (SEQ ID NO:7), or
 - (ii) an addition variant of SEQ ID NO:7 to which are thereof having an additional 1 to 4 amino acids selected from His, Pro or Gly added at the N- or C-terminus of SEQ ID NO:7, 1 to 4 amino acids selected from His, Pro and Gly,

which pentapeptide or addition variant has substantially the same transition metal ion- or plasminogen- binding activity or substantially the same biologic activity as human HPRG, rabbit HPRG, or as a polypeptide the sequence of which is SEQ ID NO:5 or SEQ ID NO:6,

which biological activity in (a) or (b) is that of inhibiting (i) angiogenesis, (ii) endothelial cell proliferation or (iii) endothelial tube formation in an *in vitro* or *in vivo* bioassay.

2. (Previously Presented) The isolated peptide of claim 1 which is

- (i) said pentapeptide of (b) with a sequence selected from the group consisting of His-His-Pro-His-Gly (SEQ ID NO:8),
His-Pro-Pro-His-Gly (SEQ ID NO:9), and
Pro-Pro-Pro-His-Gly (SEQ ID NO:10), or
- (ii) said addition variant of said pentapeptide.

3. **(Withdrawn)** A chemically synthesized peptide multimer comprising the pentapeptide or addition variant of claim 1, which multimer is selected from the group consisting of:

- (a) a multimer having the formula P^1_n wherein
 - (i) P^1 is the pentapeptide or addition variant of claim 1, and
 - (ii) $n=2-8$,
- (b) a multimer having the formula $(P^1-X_m)_n-P^2$, wherein
 - (i) P^1 and P^2 are said pentapeptides or addition variants according to claim 1,
 - (ii) P^1 and P^2 are the same or different peptides;
 - (iii) X is C₁-C₅ alkyl, C₁-C₅ alkenyl, C₁-C₅ alkynyl, C₁-C₅ polyether containing up to 4 oxygen atoms;
 - (iv) $m = 0$ or 1 ; and
 - (v) $n = 1-7$,

and wherein the peptide multimer has substantially the same ligand binding activity or biological activity of human HPRG, rabbit HPRG, SEQ ID NO:5 or SEQ ID NO:6 of inhibiting angiogenesis, endothelial cell proliferation or endothelial tube formation in an *in vitro* or *in vivo* bioassay.

4. **(Withdrawn)** A recombinantly produced peptide multimer comprising the pentapeptide or addition variant of claim 1, which multimer has the formula $(P^1-Gly_z)_n-P^2$, wherein:

- (i) P^1 and P^2 are the pentapeptides or addition variants according to claim 1,
- (ii) P^1 and P^2 are the same or different;
- (iii) $z = 0-6$; and
- (iv) $n = 1-100$,

and wherein the peptide multimer has substantially the same ligand binding activity or biological activity of human HPRG, rabbit HPRG, SEQ ID NO:5 or SEQ ID NO:6 of inhibiting angiogenesis, endothelial cell proliferation or endothelial tube formation in an *in vitro* or *in vivo* bioassay.

5. **(Previously Presented)** A diagnostically or therapeutically labeled anti-angiogenic polypeptide, peptide or variant according to claim 1 or 2.

Claim 6 (Cancelled).

7. **(Previously Presented)** A diagnostically useful HPRG-related composition comprising:

- (a) the diagnostically labeled polypeptide or peptide of claim 5; and
- (b) a diagnostically acceptable carrier.

8. **(Previously Presented)** The diagnostically useful composition of claim 7 wherein polypeptide or peptide is labeled with a detectable label is selected from the group consisting of a radionuclide, a PET-imageable agent, an MRI-imageable agent, a fluorescer, a fluorogen, a chromophore, a chromogen, a phosphorescer, a chemiluminescer or a bioluminescer.

9. **(Previously Presented)** The diagnostically useful composition of claim 8, wherein the detectable label is a radionuclide selected from the group consisting of ^3H , ^{14}C , ^{35}S , ^{67}Ga , ^{68}Ga , ^{72}As , ^{89}Zr , ^{97}Ru , ^{99}Tc , ^{111}In , ^{123}I , ^{125}I , ^{131}I , ^{169}Yb and ^{201}Tl .

10. **(Currently Amended)** The diagnostically useful composition of claims 8 wherein the detectable label is a fluorescer or fluorogen selected from the group consisting of fluorescein, rhodamine, dansyl, phycoerythrin, phycocyanin, allophycocyanin, *o*-phthaldehyde, fluorescamine, a fluorescein derivative, Oregon Green, Rhodamine Green, Rhodol Green and Texas Red.

11. **(Previously Presented)**: An anti-angiogenic pharmaceutical composition comprising:

- (a) the polypeptide or peptide of claim 1 or 2; and
- (b) a pharmaceutically acceptable carrier.

12. **(Previously Presented))** A therapeutic anti-angiogenic pharmaceutical composition comprising:

- (a) the labeled polypeptide or peptide of claim 5 to which is bound directly or indirectly a therapeutically active moiety; and
- (b) a pharmaceutically acceptable carrier.

13. **(Previously Presented)** The pharmaceutical composition of claim 11 or 12 in a form suitable for injection.

14. **(Original)** The therapeutic pharmaceutical composition of claim 12 wherein the therapeutically active moiety is a radionuclide.

15. **(Original)** The therapeutic pharmaceutical composition of claim 14, wherein the radionuclide is selected from the group consisting of ^{47}Sc , ^{67}Cu , ^{90}Y , ^{109}Pd , ^{125}I , ^{131}I , ^{186}Re , ^{188}Re , ^{199}Au , ^{211}At , ^{212}Pb and ^{217}Bi .

16. **(Withdrawn)** An antibody specific for an epitope of HPRG that is present in the H/P domain of human HPRG (SEQ ID NO:5) or the H/P domain of rabbit HPRG (SEQ ID NO:6), and which binds to HPRG or to any of said domains in a way which inhibits the anti-angiogenic activity of HPRG or said domain, or an antigen-binding fragment of said antibody.

17. **(Withdrawn)** The antibody of claim 16, wherein the epitope comprises a pentapeptide from said H/P domain having the sequence His-His-Pro-His-Gly (SEQ ID NO:8), His-Pro-Pro-His-Gly (SEQ ID NO:9), or Pro-Pro-Pro-His-Gly (SEQ ID NO:10), or an antigen binding fragment of said antibody, which antibody or fragment inhibits the anti-angiogenic activity of said pentapeptide.

18. **(Withdrawn)** The antibody of claim 16 or 17 which is a monoclonal antibody.

19. **(Withdrawn)** The antibody of claim 18 that is a human or humanized monoclonal antibody.

20. **(Withdrawn)** An antibody useful for detecting HPRG comprising the antibody or fragment of any of claims 16 or 17, which is detectably labeled.

21. **(Withdrawn)** A therapeutically useful antibody that targets HPRG or an epitope thereof, comprising the antibody or fragment of any of claims 16 or 17 to which is bound directly or indirectly a therapeutically active moiety.

22. **(Withdrawn)** A pharmaceutical composition that stimulates angiogenesis *in vitro* or *in vivo*, comprising:

- (a) the antibody or fragment of any of claims 16 or 17; and
- (b) a pharmaceutically acceptable carrier.

23. **(Withdrawn)** A method for inhibiting cell migration, cell invasion, cell proliferation or angiogenesis, or for inducing apoptosis, comprising contacting cells associated with undesired cell migration, invasion, proliferation or angiogenesis with an effective amount of a therapeutic pharmaceutical composition according to claim 11.

24. **(Withdrawn)** A method for treating a subject having a disease or condition associated with undesired cell migration, invasion, proliferation, or angiogenesis, comprising administering to the subject an effective amount of a pharmaceutical composition according to claim 11.

25. **(Withdrawn)** A method for stimulating angiogenesis comprising providing to cells participating in angiogenesis an effective amount of the antibody or fragment of any of claims 16 or 17.

26. **(Withdrawn)** A method for stimulating angiogenesis in a subject in need of enhanced angiogenesis, comprising administering to said subject an effective amount of the pharmaceutical composition of claim 22.

27. **(Withdrawn)** A method for detecting the presence of HPRG or cleavage product or peptide thereof in a biological sample, comprising the steps of:

- (a) contacting the sample with the antibody or fragment of claim 20; and
- (b) detecting the presence of the label associated with the sample.

28. **(Withdrawn)** The method of claim 27 wherein the sample is plasma, serum, cells, a tissue, an organ, or an extract of said cells, tissue or organ.

29. **(Withdrawn)** The method of claim 27, wherein the contacting and the detecting are *in vitro*.

30. **(Withdrawn)** The method of claim 27 wherein the contacting is *in vivo* and the detecting is *in vitro*.

31. **(Withdrawn)** The method of claim 27 wherein the contacting is *in vivo* and the detecting is *in vitro*.

32. **(Withdrawn)** The method of claim 27, wherein the contacting and the detecting are *in vivo*.

33. **(Withdrawn)** An isolated nucleic acid that encodes the polypeptide or peptide of claim 1 or 2 or encodes the peptide multimer of claim 4.

34. **(Withdrawn)** An expression vector comprising the nucleic acid of claim 33 operatively linked to

- (a) a promoter and
- (b) optionally, additional regulatory sequences that regulate expression of said nucleic acid in a eukaryotic cell.

35. **(Withdrawn)** The expression vector of claim 34 which is a plasmid.

36. **(Withdrawn)** The expression vector of claim 34 which is a viral vector.

37. **(Withdrawn)** A cell transformed or transfected with the nucleic acid molecule of claim 33.

38. **(Withdrawn)** A cell transformed or transfected with the expression vector of claim 34.

39. **(Withdrawn)** The cell of claim 37 which is a mammalian cell.

40. **(Withdrawn)** The cell of claim 39 which is a human cell.

41. **(Withdrawn)** A method for providing to a cell, tissue or organ an angiogenesis-inhibitory amount of a HPRG, an H/P domain of HPRG or a pentapeptide of said H/P domain having the sequence (His,Pro)-(His,Pro)-Pro-His-Gly (SEQ ID NO:7), or a peptide multimer that includes said pentapeptide, comprising
administering to said cell tissue or organ, the **expression vector of claim 34**, such that the nucleic acid is taken up and expressed in said cell, tissue or organ.

42. **(Withdrawn)** The method of claim 41 wherein said administering is *in vivo*.

43. **(Withdrawn)** A method for providing to a cell, tissue or organ an angiogenesis-inhibitory amount of a HPRG, an H/P domain of HPRG, a pentapeptide of said H/P domain having the sequence (His,Pro)-(His,Pro)-Pro-His-Gly (SEQ ID NO:7), or a peptide multimer that includes said pentapeptide, comprising
contacting said cell tissue or organ, with the **transformed or transfected cells of claim 38**, wherein said administered cells express the polypeptide, peptide or peptide multimer.

44. **(Withdrawn)** The method of claim 43 wherein said contacting is *in vivo*.

45. **(Withdrawn)** A method for inhibiting angiogenesis in a subject in need of such inhibition, comprising administering to the subject an effective amount of the expression vector of claim 34, such that said nucleic acid is expressed resulting in the presence of an angiogenesis-inhibiting amount of said polypeptide, peptide or peptide multimer, thereby inhibiting said angiogenesis.

46. **(Withdrawn)** A method for inhibiting angiogenesis in a subject in need of such inhibition, comprising administering to the subject an effective amount of the transformed or transfected cells of claim 38, which cells produce and provide in the subject an angiogenesis-inhibiting amount of said polypeptide, peptide or peptide multimer, thereby inhibiting said angiogenesis.

47. **(Withdrawn)** The method of claim 45 wherein said subject has a tumor, and said angiogenesis inhibition results in reduction in size or growth rate of said tumor or destruction of said tumor.

48. **(Withdrawn)** The method of claim 45 wherein said subject is a human.

49. **(Previously Presented)** An affinity ligand useful for binding to or isolating an HPRG-binding molecule or cells expressing the binding molecule, comprising a polypeptide or peptide according to claim 1 or 2, immobilized to a solid support or carrier.

50. **(Withdrawn)** A method for isolating a HPRG-binding molecule from a complex mixture comprising:

- (a) contacting the mixture with the affinity ligand of claim 49;
- (b) allowing any material in the mixture to bind to the ligand;
- (c) removing unbound material from the ligand; and
- (d) eluting the bound HPRG-binding molecule.

51. **(Withdrawn)** A method for isolating or enriching cells expressing a HPRG-binding site or receptor from a cell mixture, comprising:

- (a) contacting the cell mixture with the affinity ligand of claim 49;
- (b) allowing any cells expressing the binding site or receptor to bind to the affinity ligand;
- (c) separating cells bound to the compound from unbound cells; and
- (d) removing the bound cells,

thereby isolating or enriching the HPRG binding site-expressing cells.

52. **(Withdrawn)** A diagnostically or therapeutically labeled peptide multimer according to claim 3 or 4.

53. **(Withdrawn)** An anti-angiogenic pharmaceutical composition comprising

- (a) the peptide multimer of: claim 3 or 4; and
- (b) a pharmaceutically acceptable carrier.

54. **(Withdrawn)** A therapeutic anti-angiogenic pharmaceutical composition comprising

- (a) the peptide multimer of: claim 3 or 4 to which is bound directly or indirectly a therapeutically active moiety; and
- (b) a pharmaceutically acceptable carrier.

55. **(Withdrawn)** An affinity ligand useful for binding to or isolating an HPRG-binding molecule or cells expressing the binding molecule, comprising a peptide multimer according to claim 3 or 4, immobilized to a solid support or carrier.

Claims 56-57 **(Cancelled)**.